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Synthesis of (−)-Chaetominine

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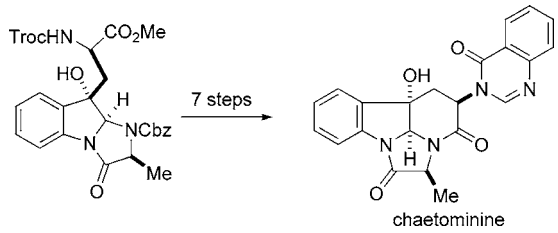
ABSTRACT



The tricyclic hydroxy imidazolidinone was converted to chaetominine in seven steps in 22% overall yield. The key step was the construction of the δ-lactam by heating an amino ester with a catalytic amount of DMAP in toluene at reflux.

Tan and co-workers recently isolated chaetominine (**1**), an alkaloid with a novel skeleton from *Chaetomium* sp. IFB-E015, an endophytic fungus found on apparently healthy *Adenophora axilliflora* leaves (see Figure 1).[1] The structure

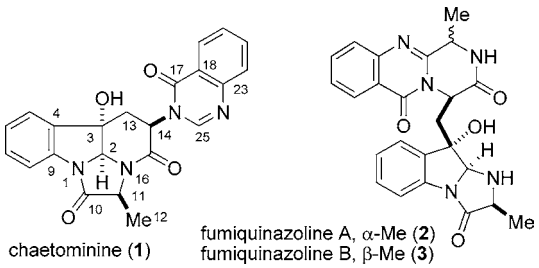


Figure 1. Structures of chaetominine (**1**) and fumiquinazolines A (**2**) and B (**3**).

was determined by both spectroscopic analysis and single-crystal X-ray diffraction analysis. The absolute stereochemistry was assigned as shown based on the release of L-alanine on acidic hydrolysis. Chaetominine is more active against human leukemia K562 (21 nM) and colon cancer SW1116 (28 nM) cell lines than 5-fluorouracil.

Chaetominine (**1**) is a modified tripeptide alkaloid containing D-tryptophan, L-alanine, anthranilic acid, and formic acid. Chaetominine is very closely related to the fumiquinazoline alkaloids such as fumiquinazolines A (**2**) and B (**3**), which are tetrapeptide alkaloids containing D-tryptophan, L-alanine, anthranilic acid, and a second alanine instead of the formic acid of chaetominine. We recently reported efficient syntheses of (−)-fumiquinazolines A, B, C, E, H, and I.[2] The key step in the syntheses is the Buchwald palladium-catalyzed cyclization of iodocarbamate **4**, which provided tricycle **5** in 64% yield (see Scheme 1). Oxidation of tricycle **5** with oxaziridine **6** in MeOH followed by reduction with $NaBH_4$ in HOAc afforded hydroxy imidazolidinone **7** in 51% yield. Treatment of **7** with silica gel resulted in cyclization to form lactone **8**, which was then elaborated to fumiquinazolines A, B, C, and E.[2]

Deprotection of the Cbz group of **7**, formation of the δ-lactam, deprotection of the Troc group, and construction of the quinazolinone should provide a short synthesis of chaetominine (**1**). However, our earlier studies indicated that formation of the δ-lactam might not be straightforward. Hydrogenolysis of the Cbz group of **7** afforded amino alcohol **9**, which was treated with silica gel in CH_2Cl_2 to give lactone **10** in 81% yield from **7**.[2] Hydrogenolysis of the Cbz group of **7** could be accomplished without hydrogenolysis of the tertiary benzylic alcohol, but hydrogenolysis of Cbz lactone

(1) Jiao, R. H.; Xu, S.; Liu, J. Y.; Ge, H. M.; Ding, H.; Xu, C.; Zhu, H. L.; Tan, R. X. *Org. Lett.* **2006**, *8*, 5709−5712.

(2) Snider, B. B.; Zeng, H. *J. Org. Chem.* **2003**, *68*, 545−563.

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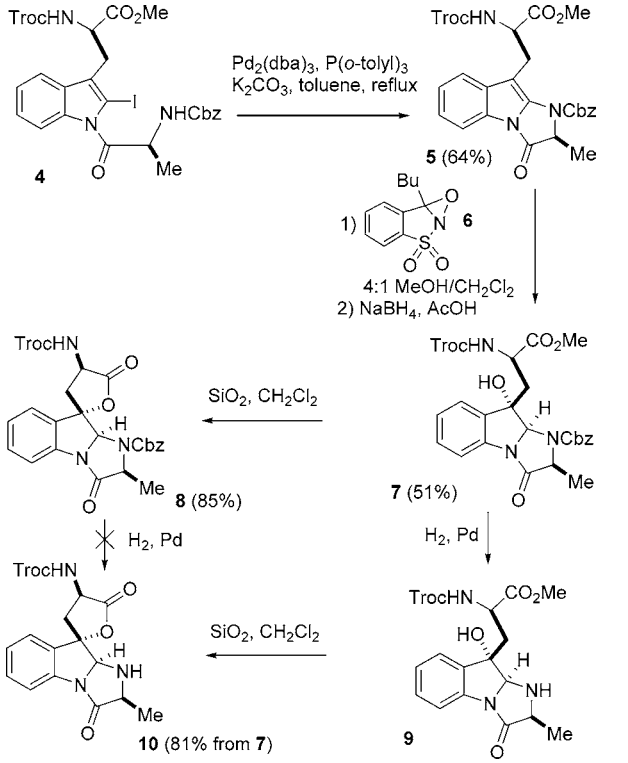
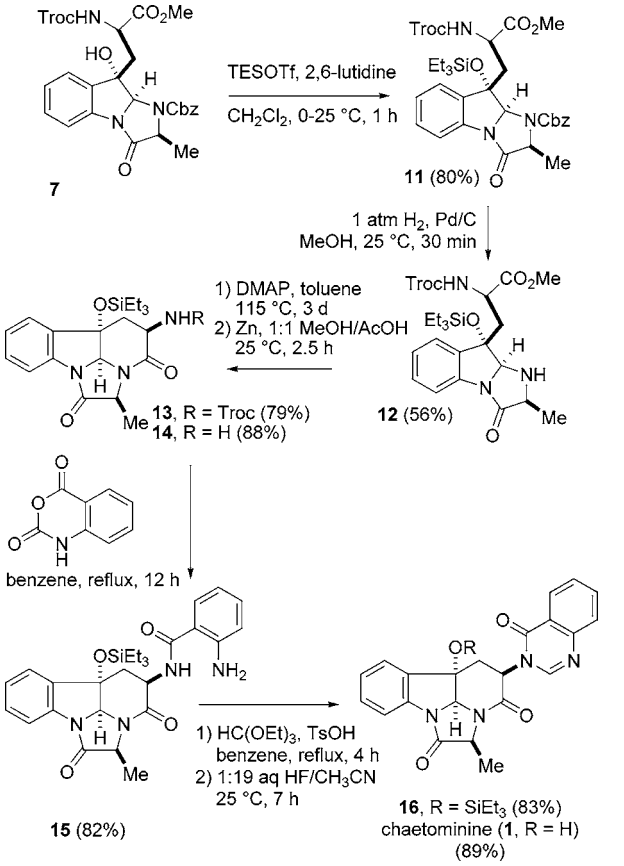
Scheme 1. Synthesis of Imidazolidinone **7**



Scheme 2. Synthesis of (−)-Chaetominine (**1**)



8 resulted in reductive cleavage of the benzylic lactone as well as the Cbz group.[2]

We explored a variety of approaches to form the desired *δ*-lactam from amino alcohol **9**. These invariably led to complex mixtures or the undesired lactone **10**. Eventually, we concluded that protection of the alcohol was necessary. Reaction of **7** with TESOTf and 2,6-lutidine in CH_2Cl_2 at 0−25 °C provided TES ether **11** in 80% yield (see Scheme 2).[3] Hydrogenolysis with 1 atm of H_2 and 10% Pd/C afforded the desired amino ester **12** in only 56% yield, suggesting that cleavage of the TES group or hydrogenolysis of the OTES group was occurring. Use of $Pd(OH)_2$ as catalyst or transfer hydrogenation did not improve the yield. We were unable to prepare more hindered silyl ethers of **7** in acceptable yield, so we proceeded with compound **12**.

Lactamization of amino ester **12** was also challenging but was eventually accomplished to give **13** in 79% yield by heating **12** in toluene containing a catalytic amount of DMAP for 3 days at reflux in a sealed tube.[4] Lactam **13** was contaminated with about 5% of two compounds that are probably diastereomers of **13**. Use of 6 equiv of Et_3N instead of catalytic DMAP gave a lower yield of **13**.[5]

Deprotection of the Troc group of **13** without cleavage of the TES ether was accomplished with Zn in 1:1 MeOH/HOAc to give amine **14** in 88% yield. Reaction of amine **14** with isatoic anhydride in benzene at reflux[6] afforded amino amide **15** in 82% yield. Reaction of **15** with excess triethyl orthoformate and a catalytic amount of TsOH in benzene at reflux[6] provided TES-chaetominine (**16**) in 83% yield. Cleavage of the TES group in 1:19 concentrated HF/CH_3CN[7] for 7 h at 25 °C provided chaetominine (**1**) in 89% yield. The yields were improved if intermediates were not purified. The four-step conversion of **13** to **1** proceeded in 62% overall yield when only amino amide **15** was purified.

The ^1H and ^{13}C NMR, IR, CD, and mass spectra of synthetic **1** are identical to those reported by Tan.[1] H_{14}, H_{19}, H_{25}, C_{13}, C_{14}, C_{17}, C_{18}, and C_{23} are very broad as noted by Tan. He attributed this to slow inversion of an sp^3 nitrogen in the quinazolinone ring. We think that this is probably a result of slow rotation about the C_{14}−N bond. Similar broadening in the ^1H and ^{13}C NMR spectra of TES ether **16** also results from slow rotation about this bond.

Tan noted that chaetominine (**1**) was unstable in acid and recrystallized it from MeOH at room temperature.[1] We found that heating **1** in MeOH at reflux for 5 h afforded a 1:1

(3) Kamenecka, T. M.; Danishefsky, S. J. *Chem.—Eur. J.* **2001**, *7*, 41−63.

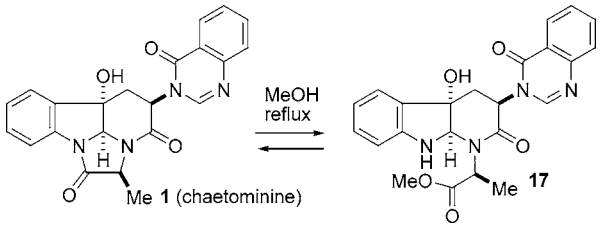
(4) For conversion of amino esters to lactams with DMAP in toluene at reflux, see: (a) Gramberg, D.; Robinson, J. A. *Tetrahedron Lett.* **1994**, *35*, 861−864. (b) Gramberg, D.; Weber, C.; Beeli, R.; Inglis, J.; Bruns, C.; Robinson, J. A. *Helv. Chim. Acta* **1995**, *78*, 1588−1606.

(5) For conversion of amino esters to lactams with Et_3N in toluene at reflux, see: (a) Dumas, J.-P.; Germanas, J. P. *Tetrahedron Lett.* **1994**, *35*, 1493−1496. (b) Tong, Y.; Olczak, J.; Zabrocki, J.; Gershengorn, M. C.; Marshall, G. R.; Moeller, K. D. *Tetrahedron* **2000**, *56*, 9791−9800.

(6) Nakagama, M.; Taniguchi, M.; Sodeoka, M.; Ito, M.; Yamaguchi, K.; Hino, T. *J. Am. Chem. Soc.* **1983**, *105*, 3709−3710.

(7) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, *20*, 3981−3982.

Scheme 3. Interconversion of Chaetominine (**1**) and Amino Ester **17**



mixture of **1** and amino ester **17** (see Scheme 3). Chromatography afforded a 6:1 mixture of **17** and **1**, which was converted to 1:1 mixture on heating in MeOH at reflux for 5 h. The conversion of **17** back to **1** establishes that the reaction is reversible and that the 1:1 mixture is at equilibrium. There are two lactams in chaetominine (**1**), and either one could be opened by MeOH to give a methyl ester. The ^{1}H NMR spectrum of **17** shows two protons at δ 6.85 (dd, 1, J = 7.6, 7.6 Hz) and 6.74 (d, 1, J = 7.6 Hz), whereas the furthest upfield aromatic hydrogen of chaetominine absorbs at δ 7.24. The upfield shift establishes that the *N*-acylindoline was cleaved to give an indoline, which has the expected upfield absorptions[8] for the protons ortho and para to the nitrogen.

The facile cleavage of the γ-lactam ring of **1** on heating in MeOH is not typical of γ-lactams and may result from the strain present in the tetracyclic core of chaetominine (**1**). The crystallographic data support this analysis. The $C_9-N_1-C_{10}=O$ and $C_2-N_1-C_{10}=O$ torsion angles in **1** are 37.8 and 175.0°, respectively (see Figure 2).[1] In the simple tricyclic

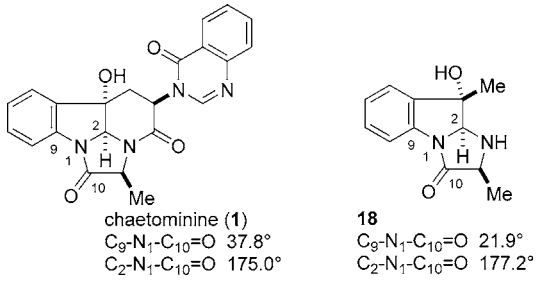
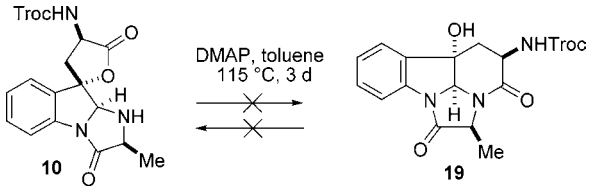


Figure 2. Torsion angles in the crystal structures of **1** and **18**.

model **18**, the torsion angles are 21.9 and 177.2°, respectively.[9] The torsion angles should be 0 and 180°, respectively, in an unstrained amide. The deformation from 21.9° in **18** to 37.8° in **1** suggests that the introduction of the δ-lactam significantly increases the strain. No reaction occurs on heating **11** in MeOH at reflux for 5 h, which supports the hypothesis that the ring strain of the tetracyclic ring system of chaetominine makes the imidazolidinone much more susceptible to cleavage. Relief of ring strain in **1** could be achieved by opening either the δ-lactam or the γ-lactam with MeOH. The inherently greater reactivity of an *N*-aryl lactam than that of an *N*-alkyl lactam may be at least partially responsible for the selective opening of the γ-lactam. The enhanced reactivity of the strained γ-lactam ring of **1** likely plays a role in its biological activity.

The strain of the tetracyclic ring system is likely responsible for the cyclization of amino alcohol **9** with SiO_2 in CH_2Cl_2 to give amino lactone **10** rather than the desired hydroxy lactam. However, it is not clear whether this is a result of kinetic or thermodynamic control. We therefore cleaved the TES ether of **13** to give hydroxy lactam **19**, which is an isomer of amino lactone **10**. Unfortunately, both amino lactone **10** and hydroxy lactam **19** decomposed on heating in toluene containing a catalytic amount of DMAP so that we were unable to determine the relative stability of amino lactone **10** and hydroxy lactam **19** (see Scheme 4).

Scheme 4. Lactone **10** and Lactam **19** Do Not Interconvert with DMAP in Toluene at Reflux



In conclusion, fumiquinazoline intermediate **7** has been converted to chaetominine (**1**) in seven steps in 22% overall yield. The key step is the cyclization of amino ester **12** with catalytic DMAP in toluene at reflux to give δ-lactam **13** in 79% yield.

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Supporting Information Available: Full experimental details and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For similar NMR spectra of related indolines, see ref 3 and: (a) Giorgio, E.; Tanaka, K.; Verotta, L.; Nakanishi, K.; Berova, N.; Rosini, C. *Chirality* **2007**, *19*, 434−445. (b) Sunazuka, T.; Shirahata, T.; Tsuchiya, S.; Hirose, T.; Mori, R.; Harigaya, Y.; Kuwajima, I.; Ōmura, S. *Org. Lett.* **2005**, *7*, 941−943.

(9) He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417−6418.